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PHARMACOECONOMIC CENTER

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Contract Announcement: Long-Acting Nifedipine (Adalat CC).....See Page

Happy New Year!

Main Points

In the absence of "red flags" that may indicate the presence of a serious underlying condition, imaging studies and further testing are not usually helpful during the first 4-6 weeks of low back symptoms.

Relief of discomfort can be accomplished most safely with nonprescription analgesics, activity modification, and/or

In This Issue

Low Back Pain

A Summary of the DoD/VA Clinical Practice Guideline for Management of Persons with Low Back Pain in Primary Care

The first guideline from the DoD/VA Clinical Practice Guideline Workgroup is now complete. A brief summary of the guideline and associated algorithm is presented in this issue of the *Update*. The guideline will be distributed to military medical treatment facilities and VA facilities and posted on the Internet; instructions for obtaining a copy of the complete guideline will be published in the *Update* as soon as it is available.

Patient Population: Patients with low back pain or sciatica 17 years of age or older.

Initial Assessment: The initial assessment is based on a focused medical history and a physical examination. The primary purpose is to look for "red flags," medical history responses or physical exam findings that suggest the presence of a serious underlying condition such as fracture, tumor, infection, or cauda equina syndrome (CES). The possibility that referred pain from visceral organs may present as low back pain should also be considered. Patient who exhibit red flags, or whose findings indicate the presence of another medical condition, should receive an appropriate and immediate work-up.

In the absence of red flags, imaging studies and further testing are not usually helpful during the first 4-6 weeks of low back symptoms. In addition, the high false-positive rate associated with radiographic studies for low back pain may lead to unnecessary concern if such studies are obtained prematurely.

The history and physical is also an opportunity for the clinician to establish rapport with the patient, explore patient expectations, and assess potential psychological and/or socioeconomic factors that could hinder the patient's successful response to treatment.

Acute Low Back Pain (< 6 weeks): In the absence of red flags or other medical conditions, treatment depends on the duration of symptoms and the type of pain (sciatica or nonspecific low back pain). For patients who have been experiencing symptoms for less than 6 weeks (acute low back pain), conservative treatment options are indicated, with a follow-up visit or phone call occurring in 1 to 3 weeks. Recommended conservative treatment options include education; activity modification; progressive range of motion and exercise; symptom control with analgesics (acetaminophen or nonsteroidal anti-inflammatory drugs (NSAIDs)); assisted management; and manipulation.

Patient education is a key component in rehabilitation. Patients should be reassured that 70% of patients with acute symptoms will be better within 2 weeks and 90% within approximately 4 weeks. Patients with sciatica may have a longer expected recovery time and require more education and assurance. Postural advice should include: avoidance of heavy lifting and repetitive bending/twisting; frequent

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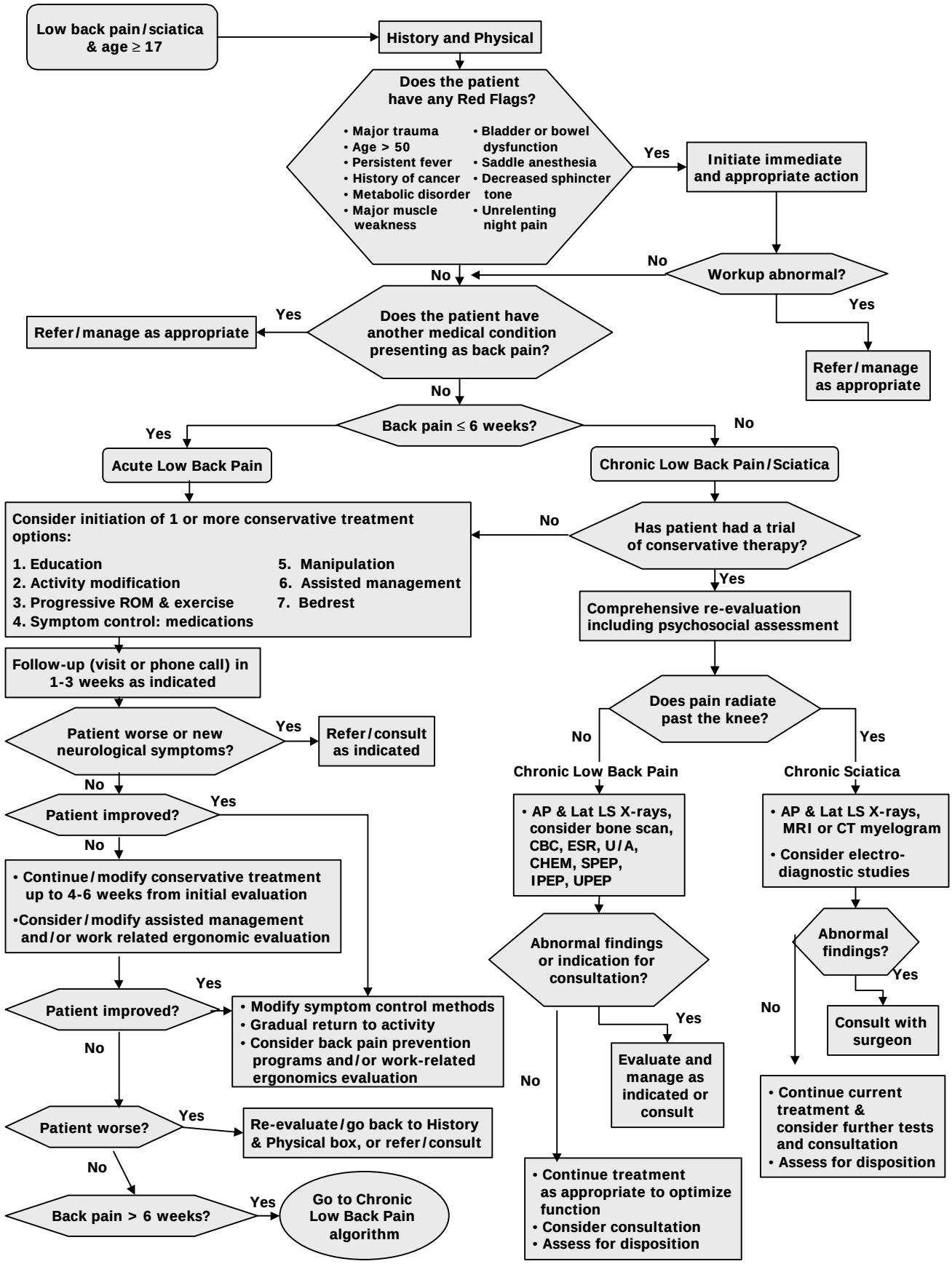
Management of Low Back Pain / Sciatica in Primary Care



DoD/VA Low Back Pain Guideline continued from Page 1

change of positions, and use of a chair with adequate lower back support. Proper body mechanics, stretching and exercise should be discussed.

Manipulation within the first 6 weeks of onset of acute low back pain has shown better short-term improvement in pain and activity levels than the treatments to which it has been compared. However, there is little evidence as to what type of manipulation is effective or which patients may be expected to benefit.

Limited bedrest (usually less than 2 days) with a graduated return to normal activities; other physical modalities; and treatment with other pharmaceutical agents (muscle relaxants, opioids, corticosteroid epidural injections) are also potentially useful options. Temporary limitation or avoidance of activities known to trigger low back pain or increase mechanical stress on the spine, such as prolonged unsupported sitting or heavy lifting, may increase patient comfort. Bedrest for more than 2-4 days is not recommended, as muscle atrophy, cardiopulmonary deconditioning, bone mineral loss, and risk of thromboembolism may result.

Opioids appear to be no more effective than other analgesics for acute low back pain and are not recommended due to the potential for severe side effects. They should be avoided if possible and, when chosen, given for a short period of time only. Muscle relaxants appear to be no more effective than NSAIDs for patients with low back symptoms; combination use of muscle relaxants with NSAIDs has not demonstrated additional benefit. Side effects including drowsiness are reported in up to 30 percent of patients taking muscle relaxants and may be especially problematic for active duty military personnel. Please see Tables 1 and 2 for doses and relative cost of acetaminophen, NSAIDs, and commonly prescribed muscle relaxants.

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Although evidence regarding the effect of exercise is limited, aerobic conditioning exercise (e.g., walking, swimming, light jogging) may be recommended to avoid debilitation. Some exercise alteration may be necessary as exercise may slightly increase low back pain symptoms. Conditioning exercises for trunk muscles are more mechanically stressful to the back than aerobic exercise and are not recommended during the first 2 weeks of symptoms, although they may be helpful later. There is limited and conflicting support for the use of any specific back exercise.

For patients who improve or do not worsen, and who do not exhibit new neurologic symptoms, conservative treatment may be continued for up to 6 weeks from the initial evaluation. Changes in NSAIDs or additional activity modification may improve symptoms. Physical therapy including instruction on gentle appropriate exercises and proper positioning, aerobic exercise and strengthening programs, back care class, group back care exercise programs, manipulation, and physical modalities (hot/cold packs, massage, ultrasound, electrical stimulation) may be helpful. Patients who improve with conservative treatment should be gradu-

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Red Flags

Factors that suggest the possibility of a serious underlying condition as the cause of acute low back pain

For Cancer or Infection:

- History of cancer
- Unexplained weight loss
- Age of patient over 50 years
- Back pain not improved with rest
- Immunosuppression
- Prolonged use of corticosteroids
- Urinary infection
- Intravenous drug use

For Cauda Equina Syndrome or Severe Neurological Compromise

- Medical history or physical exam findings of acute onset of urinary retention or overflow incontinence
- Loss of anal sphincter tone or fecal incontinence
- Saddle anesthesia (about the anus, perineum, and genitals)
- Global or progressive muscle weakness in the lower limbs

For Spinal Fracture:

- History of significant trauma
- Prolonged use of steroids
- Age of patient over 70 years

Table 1: Acetaminophen and Nonsteroidal Anti-Inflammatory Agents*

Drug	Usual Single Adult Analgesic Dose	Dose Interval (hours)	Max Daily Dose (mg)	Half-life (hrs)	Relative
Nonprescription (Over-the-counter) Agents					
Acetaminophen	325-650	Q4-6	4000	2	$
Aspirin	325-650	Q4-6	4000	6-12	$
Ibuprofen OTC (Advil, Nuprin, Motrin, others)	200-400	Q4-6	1200	2	$
Ketoprofen OTC (Actron, Orudis-KT)	12.5-25	Q4-6	75	2-4	$$
Naproxen Na OTC (Aleve, others)	220–440 initial, then	Q8-12	660	13	$$
NSAIDs on the Basic Core Formulary					
Ibuprofen	400-800	Q4-6	3200	2	$
Indomethacin immediate release (Indocin, others)	25-50	Q6-8	150	4-5	$
Naproxen (Naprosyn, others)	500 initial then 250	Q6-8	1250 on 1st day, then	13	$
Salsalate (Disalcid, others)	1000	Q8-12	4000	16	$
Other NSAIDs					
Choline Mg trisalicylate (Trilisate, others)	1000-1500	Q8-12	3000	9-17	$$
Diclofenac immediate release (Cataflam)	50 50-75	Q8 Q8-12	150 200	1-2	$$$$$ $$$
Diflunisal (Dolobid, others)	1000 initial then 500	Q8-12	1500	8-12	$$
Etodolac (Lodine, others)	200-400	Q6-8	1200	3-11	$$
Flurbiprofen (Ansaid, others)	50-100	Q6-8	300	5-7	$$
Ketoprofen (Orudis, others)	25-75	Q6-8	300	2-4	$$
Ketorolac (Toradol)***	PO: 10 IM/IV: 30mg pts < 65 yrs	Q4-6 Q6	40 120	4-7	$$$$ $$$$$
Indomethacin sustained release	75	Q12	150	4-5	$$
Nabumetone (Relafen)	1000	Q12-24	2000	24	$$$$$
Naproxen Na (Anaprox, others)	550 initial then 275 or 550	Q6-8 Q12	1375 on 1st day, then 1100	13	$
Oxaprozin (Daypro)	1200	Q24	1800	24	$$$$
Piroxicam (Feldene, others)	20	Q24	20	50	$
Sulindac (Clinoril, others)	150-200	Q12	400	8	$
Tolmetin (Tolectin, others)	200-600	Q6-8	1800	1-2	$$$

Cost for maximum daily dose

$ less than $0.25/day
$$ from $0.26 to $0.75/day
$$$ from $0.76 to $1.25/day
$$$$ from $1.26 to $2.00/day

* NSAID products with minimal usage in DoD during from 7/97-6/98 omitted (fenoprofen, mefenamic acid, meclofenamate)

** Relative cost per day at maximum daily dose based on DAPA prices as of 10-15-98 (lowest priced AB-rated generic if applicable; prices for OTC medications and products with no DAPA price in effect as of 10-15-98 based on Average Wholesale Price (AWP) or direct price from manufacturer); see key

*** Combined duration (injectable & oral) should not exceed 5 days; initial IM dose of 60 mg (< 65 yrs) or 30 mg (> 65 yrs) may be given

Table 2: Commonly Prescribed Muscle Relaxants

Drug	Usual Oral Adult Dosage	Contraindications	Relative
Muscle Relaxants on the Basic Core Formulary			
Cyclobenzaprine (Flexeril, others)	10 mg TID; not to exceed	Cardiac disease, hyperthyroidism, concomitant treatment with MAO inhibitors or within 14 days of discontinuation	$
Methocarbamol (Robaxin, others)	Initial: 1500 mg QID; mainte-		$
Others			
Carisoprodol (Soma, others)	350 mg TID & HS	Acute intermittent porphyria	$
Chlorzoxazone (Parafon Forte, others)	500-750 mg TID – QID		$
Diazepam (Valium, others)	2-10 mg TID – QID		$
Orphenadrine (Norflex, others)	100 mg BID	Glaucoma; pyloric or duodenal obstruction; stenosing peptic ulcers; prostatic hypertrophy; bladder neck obstruction; cardiospasm (megaesophagus), myasthenia gravis	$$$$
Metaxalone (Skelaxin)	800 mg TID – QID	Known tendency to drug-induced hemolytic or other anemias; significantly impaired renal or hepatic function	$$$

* At usual daily dosage based on DAPA prices as of 10-15-98; see key, Table 1

ally returned to normal activity with tapering of medications and enrolled in a back pain prevention program.

Chronic Low Back Pain (> 6 weeks): Patients who present with duration of symptoms for longer than 6 weeks should receive a course of conservative treatment if not already tried. For patients who continue to exhibit symptoms after 4-6 weeks of conservative treatment, a comprehensive re-examination including psychosocial assessment and physical examination is indicated.

Diagnostic tests are performed in order to 1) gather information on potential physiologic dysfunction (e.g., neurologic dysfunction, infection, inflammation, malignancy, other systemic illness) and 2) define an anatomic reason for the dysfunction (e.g., herniated lumbar disc, spinal stenosis, infection, tumor, abdominal mass). Whether or not pain radiates below the knee is a key question to guide the choice of diagnostic tests in order to identify patients who may benefit from surgical decompression. Recommendations for selection of imaging techniques and electrophysiological tests are included in the guideline.

Continuation of Treatment: For patients who do not exhibit abnormal findings, treatment should focus on optimizing function through a physical conditioning program designed to build activity tolerance and overcome individual limitations. Behavior modification, activity-specific education, or an organized multi-disciplinary back rehabilitation program may also be useful. NSAIDs may be used to reduce chronic low back pain. Long term use (more than 2 weeks) of opioids and muscle relaxants is not recommended. There is no conclusive evidence that antidepressant medications have a place in the care of chronic low back pain.

Manipulation has shown inconclusive results when used in chronic low back pain conditions; other physical modalities have no long-term effect on outcome. There is no evidence to support the use of shoe insoles/lifts, or lumbar corsets/supports for chronic low back pain, nor does there appear to be a role for acupuncture, epidural steroid injections, or facet joint injections for patients with chronic low back pain without specific deficits or x-ray changes. There is evidence against the use of narcotics or benzodiazepines for more than 2 weeks, systemic steroids, bed rest with traction, manipulation under general anesthesia, and use of plaster jackets.

For active duty military personnel who have not improved in 4 to 6 months, a referral to the Medical Evaluation Board for possible reclassification or discharge from service should be considered.

Comments: The DoD/VA guideline for management of persons with low back pain in primary care is consistent with and adapted from the 1994 Agency for Health Care Policy Research (AHCPR) guideline for treatment of acute lower back problems in adults,[1] available from the AHCPR Publications

1. Bigos S, Bowyer O, Braen G, et al. Acute Low Back Problems in Adults. Clinical Practice Guideline No. 14. AHCPR Publication No. 95-0642. Rockville, MD: Agency for Health Care Policy and Research, Public Health

New Drug Watch

New prescription drugs approved by the U.S. Food and Drug Administration (FDA) from mid-November through the end of 1998 include:

A highly selective COX-2 inhibitor

Celecoxib (Celebrex; Searle) was approved on December 31 for relief of the signs and symptoms of osteoarthritis and adult rheumatoid arthritis. In clinical trials, celecoxib was associated with a significantly lower risk of upper gastrointestinal ulcers detected by endoscopy over the 12– to 24–week study period than other nonsteroidal anti-inflammatory drugs (NSAIDs). This is most likely due to selective inhibition of cyclooxygenase-2 (COX-2), an enzyme that plays a role in pain and inflammation. Unlike other NSAIDs, therapeutic doses of celecoxib do not appear to inhibit cyclooxygenase-1 (COX-1), which helps maintain the normal stomach lining.

Because some doubt remains as to whether celecoxib actually causes fewer serious gastrointestinal complications than other NSAIDs, product labeling will include the standard warning about risks associated with all NSAIDs, including GI ulceration, bleeding and perforation.

A new drug application for another COX-2 inhibitor, rofecoxib (Vioxx; Merck), was submitted to the FDA in late November.

A depot formulation of octreotide

Octreotide acetate suspension for injection (Sandostatin LAR Depot; Novartis) was approved November 25 for the reduction of growth hormone and IGF-1 in acromegaly; the suppression of severe diarrhea and flushing associated with malignant carcinoid syndrome; and the treatment of profuse watery diarrhea associated with VIPomas (vasoactive intestinal peptide secreting tumors). The depot is recommended for use only in patients who respond to and tolerate initial treatment with subcutaneous injections of octreotide.

Sandostatin LAR Depot is administered by intragluteal injection every four weeks, with a recommended starting dose of 20 mg. For carcinoid and VIPoma patients, subcutaneous injections of octreotide should be continued for at least the first 2 weeks of depot therapy.

In this issue

A new HIV antiretroviral

Ziagen (abacavir; Glaxo Wellcome), a nucleoside analogue reverse transcriptase inhibitor, was approved on December 17 for combination treatment of HIV_1 infection in adults and pediatric patients older than 3 months of age. Abacavir is associated with a potentially fatal hypersensitivity reaction in at least 5 percent of patients; typically within the first six weeks of therapy during clinical trials. Symptoms may include skin rash, fever, nausea, abdominal pain, and severe tiredness. An abacavir hypersensitivity reaction registry has been established (1-800-270-0425) for physicians to register patients who have developed hypersensitivity symptoms with abacavir. The drug is to be dispensed to patients with a warning card containing a written list of hypersensitivity symptoms and a medication guide.

Abacavir is available in tablet and liquid form, and is taken twice daily. A product specific website for abacavir has been posted by Glaxo Wellcome at www.ziagen.com.

Lamivudine for chronic hep B

Lamivudine tablets and oral solution (Epivir-HBV; Glaxo Wellcome) were approved on Dec 8 for the treatment of adults with chronic hepatitis B associated with evidence of hepatitis B viral replication and active liver inflammation. Testing for HIV is advised prior to beginning treatment with the drug and periodically during treatment, as Epivir-HBV contains a lower dose of lamivudine than is required for treatment of HIV infection. Epivir-HBV treatment in patients with HIV infection is inappropriate due to rapid development of HIV resistance. Epivir-HBV is available in 100 mg tablets and a 5 mg/mL oral solution; recommended adult dosage in patients with normal renal function is 100 mg once daily.

Extended release oxybutynin as a once daily treatment for overactive bladder

Ditropan XL (ALZA Corp) was approved on December 17 for the treatment of overactive bladder with symptoms of urge urinary incontinence, urgency, and frequency. The once-daily controlled release formulation is expected to decrease the incidence of side effects compared to immediate release oxybutynin and to increase patient compliance with therapy. Another new agent for overactive bladder, tolterodine (Detrol)

New Drug Watch continued from Page 6

was approved by the FDA in March 1998. Product information for Ditropan XL is available at www.ditropanXL.com.

A non-amphetamine drug for narcolepsy

The FDA has approved modafinil (Provigil; Cephalon) as a Schedule IV drug to improve wakefulness in patients with excessive daytime sleepiness associated with narcolepsy. The mechanism of action of modafinil is unknown, as the drug does not appear to bind to most of the clinically relevant receptors known to be involved in sleep/wake regulation. Modafinil may affect several P-450 metabolic pathways; product labeling lists a number of potential drug-drug interactions.

Chronotherapeutic formulation of verapamil

A controlled onset formulation of verapamil designed for bedtime dosing, Verelan PM (Elan/Schwartz Pharma), was approved November 25 for the management of essential hypertension. Both Verelan PM and Searle's currently marketed verapamil product, Covera HS, have delivery systems that delay the release of verapamil for 4-5 hours, resulting in maximum plasma concentrations in the morning hours.

Contract Announcements

Diltiazem Extended Release Contract Now in Effect

The mandatory source contract for extended release diltiazem took effect on 15 December 1998, with Tiazac (Forest Pharmaceuticals) as the selected agent. The contract will allow DoD to meet the clinical needs of patients requiring extended-release diltiazem while providing DoD prescribers and patients with uniform access to the same extended release diltiazem product, regardless of geographic location. The contract is for a base year with four (4) option years.

Tiazac is indicated for the treatment of hypertension and angina. FDA approved labeling for Tiazac states that hypertensive or anginal patients treated with other formulations of diltiazem may be safely switched to Tiazac at the nearest equivalent total daily dose.

Conversion from other extended-release diltiazem products to Tiazac may be facilitated by the use of educational materials available from vendor representatives. Forest Pharmaceuticals offers informational tools for prescribers and patients that are designed to answer prescribers' dosing and safety questions and to help patients identify the new medication. For information, call:

Brian Zentz
Manager, Federal Government Accounts
Forest Pharmaceuticals
Phone: (217) 625-7563
Voice Mail: (888) 430-5227, ext. 42103

Adalat CC Voluntary Price Reduction

- A Blanket Purchase Agreement (BPA) has been signed providing for a voluntary price decrease for long-acting nifedipine (Adalat CC; Bayer). The price for Adalat CC is now $0.40 per tablet for all dosage strengths in 100, 1000, and 2000 count bottles. This price is effective immediately.
- Annual cost avoidance due solely to the reduction in price for Adalat CC is estimated at $557,500. Further savings are anticipated as use of Adalat CC increases.
- Adalat CC is the BCF selection for a long acting nifedipine product. All MTFs must carry Adalat CC on their formularies. Facilities may also include Procardia XL on their formularies in addition to Adalat CC if they so desire.

Annual Cost Avoidance:

Price Comparison: Adalat CC *versus* Procardia XL

Strength	Procardia XL prices (10/15/98	Old Adalat CC prices (10/15/98	New Adalat CC prices now in effect	Difference in cost between Procardia XL and Adalat	% Difference between Procardia XL & Adalat
30 mg	$0.653	$0.461	$0.40	-$0.253	-38.7%
60 mg	$1.167	$0.461	$0.40	-$0.767	-65.7%
90 mg	$1.191	$0.461	$0.40	-$0.791	-66.4%

Contract Status Update

Drug Product or Class	Scope of Contract	Contracting Agency	Anticipated Award Date	Estimated Annual Cost Avoidance to DoD	BCF Status
Hepatitis A vaccine	DoD	DSCP	Awarded Effective 10/1/98	$282,718	Not on BCF
Albuterol inhalers	DoD and DVA	DSCP	Awarded Effective 11/16/98	$568,000	Key/Warrick brand of albuterol inhaler specified on the BCF; must be purchased by MTFs whenever albuterol inhalers are required
Cimetidine	DoD and DVA	NAC	Awarded Effective 11/16/98	$225,000 – $350,000 depending on method of calculation	Sidmak brand of cimetidine specified on the BCF; must be purchased by MTFs whenever cimetidine is required
Ranitidine	DoD and DVA	NAC	Awarded Effective 12/1/98	$764,983 – $7.3 million depending on method of calculation	Geneva brand of ranitidine specified on the BCF; must be purchased by MTFs whenever ranitidine is required
Diltiazem XR	DoD and DVA	NAC	Awarded Effective 12/15/98	$ 5.7 million	BCF selection; single source supplier; Tiazac is the only long-acting (once-daily) diltiazem product that may be carried on MTF formularies
Long-acting nifedipine	DoD	None	BPA effective 12/1/98 See announcement	$557,500 +	Adalat CC is specified as the BCF selection for a long-acting nifedipine agent; MTFs must carry Adalat CC on their formularies. MTFs may include Procardia XL on their formularies in addition to Adalat CC if they so desire.
Alpha blockers	DoD and DVA	DSCP	January 1999		Single agent to be selected for the BCF; alpha blocker class to remain open
Fluoro-	DoD and DVA	NAC	January 1999		One or more fluoroquinolones to be selected for the BCF
Ibuprofen	DoD and DVA	NAC	January 1999		One brand of ibuprofen to be selected for the BCF
Lisinopril	DoD	DSCP	February 1999		One brand of lisinopril to be selected for the BCF
Captopril	DoD and DVA	NAC	February 1999		One brand of captopril to be selected for the BCF
Blood glucose	DoD	DSCP	February 1999		One brand of blood glucose test strips to be selected for the BCF; class to be closed
Proton pump	DoD	DSCP	February 1999		One proton pump inhibitor to be selected for the BCF; class to be closed
Statins	DoD	DSCP	GAO protests pending; March 1999		One or two HMG CoA reductase inhibitors (statins) to be selected for the BCF; class to be closed
SSRIs	DoD	DSCP	March 1999		One agent to be selected for the BCF; SSRI class to remain open
Insulin	DoD and DVA	DSCP	March 1999		One brand of insulin to be selected for the BCF

For More Information on Contracting Initiatives:

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